

Appl. No. 09/975,317  
Amendment dated: August 22, 2005  
Reply to OA of: December 22, 2004

### **REMARKS**

Applicants have amended the claims to more particularly define the invention taking into consideration the Final Rejection and the further telephone conversation with Examiner Hartley. The application has been restricted to the subject matter of claims 75, 82 and 83 combined in new claim 96. These claims have been canceled from the application without prejudice or disclaimer as have other claims which are no longer appropriate in view of new independent claim 96.

Since the limitation from claim 83 has been added to new claim 96, the anticipation rejection set forth in the Final Rejection has been obviated since all claims rejected as anticipated have been canceled from the application. Accordingly, it is most respectfully requested that the rejection on the grounds of anticipation under 35 U.S.C. 102(b) with respect to the Rocklage U.S. Patent 5,190,744 be withdrawn.

This is similarly true with respect to the rejection of claim 78 as being unpatentable over Rocklage in view of Goldenberg. Accordingly, in view of the amendments to the claims, it is most respectfully requested that these rejections be withdrawn.

The rejection of claims 83-86 under 35 U.S.C. 103 as being unpatentable over Rocklage 5,190,744 in view of Rocklage 4,889,931 has been obviated by Applicants' amendments to the claims and for the reasons already of record.

During the prosecution of this application, it has been urged by the Examiner that Rocklage discloses a method of detecting myocardial ischemia in a subject comprising administering a contrast media comprising a manganese complex and subjecting the subject to a fast MRI technique to detect abnormal blood flow. Specific reference was made to the abstract.

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In addition, it has been urged in the Official Action that methods of fast MRI, as claimed are disclosed in column 2, lines 10+ and manganese chelates are disclosed with a reference to column 4, line 55 and claim 26.

The specific dosages are said to be within the claim limits. It is urged that since the chelates are used, as encompassed by the instant claims, the metal complexes thereof would inherently be expected to have the same values as claimed. The contrast agents include pharmaceutical compositions containing calcium complexes, buffers, antioxidants, etc. as claimed with reference to column 6. However, none of these teachings provide the necessary motivation to combine the references to arrive at the presently claimed invention. Applicants' specification may not be used as a teaching reference and obvious to try is not the standard of obviousness under 35 USC 103(a).

More particularly, Applicants again wish to point out that the method claimed is not that suggested or described in Rocklage '744. Firstly, the present invention relates to the detection of myocardial ischemia whereas Rocklage '744 is concerned with the detection of cerebral (brain) ischemia. Although Rocklage '744 also teaches that the same method would be useful in the detection of coronary ischemia, the myocardium and coronary arteries are different parts of the heart - the myocardium is the middle muscular layer of the heart wall, and coronary arteries surround the heart and branch out from the aorta to supply blood to the heart. Rocklage '744 does not therefore describe a method of detecting myocardial ischemia as in the presently claimed invention.

Secondly, the specific method claimed in claim 96 can be further distinguished from the prior art. Rocklage '744 does not disclose a method of distinguishing between reversibly injured tissue and irreversibly injured tissue. It describes only a method for detecting ischemia. Ischemia is a decrease of blood supply which leads to an inadequate supply of oxygen where the blood supply is limited. The contrast agents described in Rocklage '744, in particular the Dy-compounds described in the Examples

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of '744, are blood pool agents and are detected in the blood supply by MRI. As a result, the method described in Rocklage '744 can only be used to identify and/or monitor abnormal or modified blood flow. The method does not involve or allow for the detection of damaged tissue.

On the other hand, independent claim 96 of the present application is directed to a method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue. Ischemia leads to the damage of tissue to which the patient's blood supply has been affected. The extent of the tissue damage within a patient can vary such that the damage to some tissue is reversible, whereas the damage to other tissue is not. Claim 96 is limited to a method for distinguishing between these types of tissue following/during an ischemic event. Such a method is nowhere disclosed or suggested in Rocklage '744.

The method claimed in the present application relies on the contrast agent used being able to distinguish between reversibly and irreversibly injured myocardial tissue. This is achieved using the contrast agents defined in the claims. The manganese contrast agents described in the present application dissociate once they have been administered into the body and the resulting manganese ions are able to enter viable (i.e. repairable) myocardial cells via  $\text{Ca}^{2+}$  channels. It should be noted that not all metal ions are capable of being taken up by cells via  $\text{Ca}^{2+}$  channels. The manganese ions are not however able to enter myocardial cells which are irreversibly damaged. The manganese ions generate a signal in MRI imaging, thereby generating a signal in the viable myocardial cells. Since manganese ions cannot be taken up by irreversibly damaged cells, no such signal is generated in necrotic (infarcted) cells.

The method claimed in present claim 96 is therefore able to distinguish between the two types of cells. Rocklage '744 does refer to manganese ions. However, this reference forms part of the general teaching provided by the document. The reference to manganese ions in Rocklage '744 cannot be considered prejudicial to the novelty or

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obviousness of the claims since Rocklage '744 does not disclose a method for distinguishing between reversibly and irreversibly injured myocardial tissue as discussed above. It should be noted that only Dy-contrast agents are employed in the Examples of Rocklage '744, and Dy-contrast agents are not suitable for detecting the viability of myocardial cells. This is because Dy-contrast agents are taken up neither by viable myocardial cells nor by irreversibly damaged myocardial cells. Consequently, a method employing such contrast agents is not able to distinguish between the two types of cells.

The method as claimed in claim 96 can therefore be distinguished from the methods described in the prior art. Furthermore, it is submitted that the claimed method is not obvious since a method for distinguishing reparable myocardial cells from irreparable cells is nowhere disclosed in the prior art. None of the prior art documents even address the problem of distinguishing reparable cells from irreparable cells. Furthermore, neither is there anything in the prior art to suggest that manganese contrast agents would dissociate when administered to a patient, nor that the resulting manganese ions would be taken up by viable myocardial tissue and not by necrotic tissue. The skilled person would not therefore be led to the claimed method from the cited prior art. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In addition, the limitations in the dependent claims need to be taken into consideration. These are further limitations which cannot be ignored and must be suggested by the prior art to one of ordinary skill in the art to which the invention pertains. Obvious to try is not the standard of obviousness for one of ordinary skill in the art to which the invention pertains and which is the standard applied to 35 USC 103 by the reviewing Board and the Courts. The deficiencies of the primary reference is not overcome the teachings of the secondary '131 reference. Accordingly, the rejections of the dependent claims should also be withdrawn.

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In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

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REF:kdd  
A04.wpd

August 22, 2005